Placental Mesenchymal Stromal Cells: Preclinical Safety Evaluation for Fetal Myelomeningocele Repair.

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Public Summary:
Myelomeningocele (MMC), the most severe form of spina bifida (SB), is a birth defect that occurs due to the incomplete closure of the neural tube during early pregnancy. The spinal cord is thus exposed to chemical damage from the amniotic fluid and mechanical damage from the uterine wall for the remainder of the pregnancy term, incurring additional damage. This congenital injury results in lifelong paralysis. The current standard of care treatment for MMC is fetal surgical closure of the defect. However, the fetal surgery treatment results in only 44.8% of treated children who are able to walk independently at 30 months of age. Our group aims to reverse the MMC associated paralysis and improve motor function outcomes in MMC children by augmenting the current standard of care surgery with a stem cell regenerative product. Placenta-derived mesenchymal stromal cells (PMSCs), isolated from human donors, have neuroprotective abilities that have been shown to improve motor function in our gold-standard fetal sheep model of MMC. We have developed a PMSC product under current Good Manufacturing Practices (cGMP), as required by the FDA, by seeding human clinical-grade PMSCs on a dural extracellular matrix (ECM), generating the PMSC-ECM stem cell product we aimed to evaluate for safety in this study. The PMSC-ECM product was evaluated for safety in an immunocompromised mouse model, NID/SCID/Gamma-/- (NSG). Two experimental groups were evaluated, a total of 54 mice. One group of NSG mice (26 mice) received the PMSC-ECM patch subcutaneously (placed under the skin), and the other group of NSG mice (28 mice) received just an ECM patch subcutaneously. Both groups of mice were monitored for tumor formation at 4 weeks and 6 months post-implantation of the patches. We hypothesized that the clinical-grade PMSC-ECM product would not cause any tumor formation in the immunocompromised mice at 4 weeks or at 6 months. We also hypothesized that there would be no presence of human DNA to indicate the persistence of human PMSCs in the mouse system. Pathology and histology were performed to evaluate for tumors, and results showed no evidence of any tumor development. Quantitative polymerase chain reaction (qPCR) was done to look for human DNA, which would indicate the presence of human PMSCs. Results showed no evidence of human DNA to indicate the persistence of human PMSCs at either study end points of 4 weeks or 6 months. These results support our hypothesis and the overall safety of the PMSC-ECM product to proceed to be evaluated in a Phase 1/2a human clinical trial.

Scientific Abstract:
BACKGROUND: Myelomeningocele (MMC) is the congenital failure of neural tube closure in utero, for which the standard of care is prenatal surgical repair. We developed clinical-grade placental mesenchymal stromal cells seeded on a dural extracellular matrix (PMSC-ECM), which have been shown to improve motor outcomes in preclinical ovine models. To evaluate the long-term safety of this product prior to use in a clinical trial, we conducted safety testing in a murine model. METHODS: Clinical grade PMSCs obtained from donor human placentas were seeded onto a 6 mm diameter ECM at a density of 3 x 10(5) cells/cm(2). Immunodeficient mice were randomized to receive either an ECM only or PMSC-ECM administered into a subcutaneous pocket. Mice were monitored for tumor formation until two study endpoints: 4 wk and 6 mo. Pathology and histology on all tissues was performed to evaluate for tumors. Quantitative polymerase chain reaction (qPCR) was performed to evaluate for the presence of human DNA, which would indicate persistence of PMSCs. RESULTS: Fifty-four mice were included; 13 received ECM only and 14 received PMSC-ECM in both the 4-wk and 6-mo groups. No mice had gross or microscopic evidence of tumor development. A nodular focus of mature fibrous connective tissue was identified at the subcutaneous implantation pocket in the majority of mice with no significant difference between ECM only and PMSC-ECM groups ($P = 0.32$ at 4 wk, $P > 0.99$ at 6 mo). Additionally, no human DNA was detected by qPCR in any mice at either time point. CONCLUSIONS: Subcutaneous implantation of the PMSC-ECM product did not result in tumor formation and we found no evidence that PMSCs persisted. These results support the safety of the PMSC-ECM product for use in a Phase 1/2a human clinical trial evaluating fetal MMC repair augmented with PMSC-ECM.

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